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Microvascular Disease and Risk of Cardiovascular Events Among Individuals With Diabetes: a Population-Level Cohort Study

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ABSTRACT

Background

Diabetes confers a 2-fold excess risk of atherosclerotic cardiovascular disease (ASCVD), yet predicting individual risk remains challenging. The effect of total microvascular disease burden on ASCVD risk among individuals with diabetes is unknown.

Methods

A population-based cohort of patients with type 2 diabetes from the UK Clinical Practice Research Datalink was studied (n=48 367). We used multivariable Cox models to estimate the hazard ratios for ASCVD (fatal and non-fatal events of myocardial infarction or ischemic stroke) associated with cumulative burden of retinopathy, nephropathy and peripheral neuropathy among individuals with no history of cardiovascular disease at baseline.

Results

During a median follow-up of 5.5 years, 2689 (5.6%) individuals experienced a cardiovascular event. Significant associations were observed for ASCVD individually for retinopathy, peripheral neuropathy, and nephropathy after adjustment for established risk factors. The hazard ratios (with 95% confidence intervals) were 1.16 (1.06-1.27), (1.26, 1.16-1.38), and (1.49, 1.36-1.62), respectively. For individuals with one, two or three microvascular disease states versus none, the multivariable-adjusted hazard ratios for ASCVD were 1.30 (1.16-1.47), 1.64 (1.45-1.87) and 2.24 (1.91-2.64), respectively. The hazard ratios for fatal cardiovascular events and hospitalization for heart failure were similar. For ASCVD, measures of risk discrimination showed significant improvement when microvascular disease was added to models.

Conclusions

The cumulative burden of microvascular disease significantly impacts the risk of future cardiovascular disease among individuals with type 2 diabetes. Given the prevalence of diabetes globally, further work to understand the mechanisms behind this association and strategies to mitigate this excess risk are warranted.

INTRODUCTION

Diabetes confers a 2-fold excess risk of cardiovascular disease[1] and substantial premature mortality from cardiovascular causes.[2] However, individuals with diabetes are not automatically considered as a coronary heart disease (CHD) risk equivalent and many guidelines now recommend absolute risk assessment prior to considering lipid modification therapy.[3] Predicting individual risk remains challenging and external validation of available risk algorithms in diabetic populations show moderate performance at best,[4] highlighting the need for cheap and routinely available measures that identify those with higher absolute risk over and above established factors considered in contemporary risk algorithms.

Various microvascular disease states have been reported to be associated with risk of vascular disease, including cardiac autonomic neuropathy (CAN),[5, 6] retinopathy,[7, 8] nephropathy,[9] and peripheral neuropathy.[10] Despite frequently co-existing, robust population data evaluating the effect of cumulative microvascular disease burden on cardiovascular risk in diabetes is absent. The aim of this study was to investigate whether microvascular disease states alone or in unison are independently associated with atherosclerotic cardiovascular disease (ASCVD), and furthermore to compare any strength of association with conventional risk factors used in current risk equations. To assess this relationship, we used routine healthcare data from a large population-based cohort of individuals with type 2 diabetes free from CVD at baseline, with approximately 259 686 person years of follow up and 2689 first cardiovascular events.

METHODS

Data sources and cohort

The Clinical Practice Research Datalink (CPRD) comprises data on individuals from over 600 practices in England, providing a representative UK primary care population.[11, 12] CPRD contains information on anthropometric measurements, clinical diagnoses, laboratory tests and prescription data, coded with the Read Clinical Coding system. Information on retinopathy, nephropathy and peripheral neuropathy has been routinely collected in UK primary care following the introduction of a pay for performance initiative, the Quality and Outcomes Framework,[13] in April 2004, which is linked to the National Institute for Health and Care Excellence (NICE) guidance on standards of care for patients in the UK including appropriate frequency of screening and risk factor control for those with chronic diseases.[14]

Individual patient data were linked across three datasets: the CPRD for demographic characteristics and, Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) for the outcomes of interest. The HES are the English National Health Service administrative dataset and contain information on every hospital admission including diagnostic data, recorded as International Classification of Diseases, 10th revision (ICD-10), and procedural data based on the Office of Population, Census, and Surveys, version 4

(OPCS-4) codes. The ONS provide individual mortality records including cause of death (ICD-10).

The study start date was 1 April 2008 to allow for 4 years of quality data on microvascular disease status among participants. The data extract provided by CPRD included data on 48 367 individuals aged 18 years and over with type 2 diabetes and complete information on the presence or absence of three microvascular diseases: retinopathy, nephropathy and peripheral neuropathy. Individuals were screened for the presence of diabetes using established criteria,[15] and classified in accordance with methods described previously.[16] Diabetes was defined by fasting plasma glucose ≥126 mg per deciliter (7.0 mmol per liter), random plasma glucose ≥200 mg per deciliter (11.1 mmol per liter) or the use of glucose lowering medications, based on recommendations from the American Diabetes Association.[15, 17] In brief, classification of T2DM was performed according to the following criteria: specific diagnostic code for T2DM (Read code C10F; ICD-10 code E11) with no contradictory code; and patients with a diagnosis of diabetes at ≥35 years of age with no insulin prescription within 1 year of diagnosis. Validation study of electronic health records using this approach corrected miscoding of diabetes type in between 6-8% of cases.[16] We excluded individuals with a prior history of any cardiovascular disease.

Definition of baseline variables

Anthropometric measurements and numerical data, including systolic and diastolic blood pressure, glycated hemoglobin, and cholesterol values were derived by taking the mean of the three most recent values in the 12 months prior to the study start date. In cases where three values were unavailable, the mean of two values was calculated. Values recorded more than 12 months prior to the study start were not considered. Smoking status was stratified into groups of never smoked, previously smoked and currently smoking at entry into the study. Code lists used to define microvascular disease states were developed in accordance with published guidance,[18, 19] and are provided in the Supplementary Appendix 1-3).

Outcome ascertainment

The follow-up period extended to the study end: either December 2014, the date of patient transfer from an included practice, or death. The primary outcome was the time to first major atherosclerotic cardiovascular event (an a priori composite of fatal and non-fatal events of MI or ischemic stroke). Information about cause-specific mortality and date of death was obtained through the established record linkage with ONS. Fatal MI and stroke were defined by primary cause of death (ICD-10 codes I21-I22 and I64 respectively). Patients were censored on the date of first ASCVD event. The pre-specified secondary endpoints were cardiovascular death (fatal MI or fatal ischemic stroke), hospitalization for heart failure and all-cause mortality. Study approval was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency.

Statistical analyses

We defined clinical characteristics and outcome data both overall and according to risk groups (absence of microvascular disease at baseline, or stratified by the number of prevalent microvascular disease states). All reported P values are two-sided. Adjusted hazard ratios and corresponding 95% confidence intervals were estimated with Cox proportional-hazards models. Adjustment in all models was performed for age, gender, on treatment systolic and diastolic blood pressure, high- and low-density cholesterol, HbA1c, body-mass index, smoking status, index of multiple deprivation, antiplatelet, lipid-lowering and renin angiotensin blockade therapy. The group free of microvascular disease at baseline were used as the reference category.

We assessed differences in predictive accuracy of a model including established risk factors from the Framingham risk function for a first CVD event (model A),[20] and the same model incorporating microvascular disease variables (model B) for ASCVD events. Model discrimination was assessed with the use of the C-statistic.[21] To evaluate the overall improvement in risk stratification with the addition of microvascular disease to fully adjusted models, we calculated net reclassification improvement statistic and the integrated-discrimination-improvement statistic.[22] Risk strata were as defined in the American College of Cardiology (ACC)/ American Heart Association (AHA) treatment guidelines for 10-year ASCVD risk (low-risk <5%, intermediate-risk 5-7.5%, and high-risk >7.5%)[3] Statistical analyses were performed with the use of R software version 15.2.

RESULTS

Patient Characteristics

Baseline characteristics of the study population, both overall and according to microvascular disease burden, are shown in Table 1. Individuals with microvascular disease were more likely to have an adverse cardiovascular risk profile with significantly greater levels of HbA1c and systolic blood pressure and worse renal function. Age and duration of diabetes significantly increased in a linear fashion with increasing burden of microvascular disease. Exceptions included a consistent trend for more favourable lipid parameters with increasing burden of microvascular disease, likely related to the greater use of lipid-lowering therapy. A comparison of the demographic characteristics of individuals with a single manifestation of microvascular disease versus those without is provided in the Supplementary Appendix 4.

Primary and Secondary Outcome Measures

Event rates of ASCVD per 1000 person years in those without microvascular disease were 5.73 compared with 8.90, 9.14 and 11.63 among individuals with isolated retinopathy, nephropathy and peripheral neuropathy, respectively. Each microvascular disease state studied was significantly associated with ASCVD, and remained so following adjustment for

established risk factors and after excluding individuals with multiple manifestations of microvascular disease (Table 5 in the Supplementary Appendix). Single manifestations of microvascular disease appear to confer at least as much risk as the failure to control conventional risk factor goals in adjusted analyses (Supplementary Appendix 6-8).

Figure 1 shows the linear relationship between increasing burden of microvascular disease and ASCVD (Panel A), cardiovascular mortality (Panel B), and hospitalization for heart failure (Panel C), P for linear trend <0.001 for all. Analyses for all-cause mortality were qualitatively similar (Supplementary Appendix 9); we found a 3.9-fold excess risk of death from any cause among individuals with three manifestations of microvascular disease compared with none (Supplementary Appendix 10). Unadjusted event rates for ASCVD among individuals free of microvascular disease at baseline and among those with one, two, or three microvascular disease states were 5.7, 10.4, 15.5 and 22.5 per 1000 person years, respectively. After adjustment for potential confounders, the hazard ratios for ASCVD, cardiovascular death and hospitalization for heart failure remained significant but were attenuated across all three groups, suggesting that conventional risk factors account, in part, for the excess risk observed with cumulative burden of microvascular disease (Table 2).

In fully adjusted models, a single manifestation of microvascular disease appears to as strongly associated with ASCVD as blood pressure, low-density cholesterol, glycated hemoglobin and smoking history (Figure 2). A similar relationship was observed for cardiovascular death, hospitalization for heart failure (Figure 2), and death from any cause (Supplementary Appendix 11). This association remained when established risk factors were dichotomised to reflect recommended risk factor goals and even when eGFR was included in models (Supplementary Appendix 12). When assessed across strata of risk factor control for HbA1c (<7.0%, and ≥7.0%), low-density cholesterol (<100, and ≥100 mg per decilitre) and blood pressure (<140/90, and ≥140/90 mm Hg), a consistent linear trend of greater risk of ASCVD with cumulative burden of microvascular disease and uncontrolled risk factors was observed (Figure 3).

The addition of information on microvascular disease (model B) to a Cox model based on established risk factors included in the Framingham model (model A), yielded improvements in the C-statistic (0.715 versus 0.700, respectively) and integrated discrimination index (0.004, 95% CI, 0.004-0.005, P<0.001). Across the three categories of ASCVD risk studied, the overall net reclassification improvement was 0.05 (95% CI, 0.04 to 0.06, P<0.001).

DISCUSSION

In a population cohort of individuals with type 2 diabetes, our findings show that burden of microvascular disease is a determinant of future cardiovascular risk. The risk of a first cardiovascular event increased linearly with the number of manifestations of microvascular disease present. Furthermore, the presence of isolated retinopathy, peripheral neuropathy, or nephropathy confer at least a similar risk of cardiovascular events as factors contained in contemporary risk equations such as blood pressure, low-density cholesterol and haemoglobin A1c. Despite significant differences in baseline values of glycated haemoglobin, low-density cholesterol and blood pressure among individuals with increasing burden of microvascular disease, these factors did not modify associations between microvascular disease and cardiovascular outcomes. We noted no deviations from linearity in subgroups stratified by varying degrees of risk factor control.

Consistent with our findings, previous reports have documented an increase in cardiovascular risk with individual microvascular disease states.[5-10] However, the true impact of microvascular disease may have been overestimated because risk ratios provided in the literature are subject to confounding by a lack of adjustment for the presence of disease in multiple microvascular beds. An important advance of this study was our ability to examine the effect of both cumulative burden, and isolated microvascular disease states on first presentation of cardiovascular disease. This approach was enabled by the routine collection of microvascular disease data in the UK, and the availability of electronic health record linkage.

Although event rates in type 2 diabetes are falling and do not suggest a CHD risk equivalent as previously described,[23, 24] lifetime risk remains high emphasizing the need to identify early markers of risk.[25] At diagnosis of type 2 diabetes, the UK Prospective Diabetes Study identified retinopathy alone in 36% of participants.[26] Currently, data recorded on the presence or absence of retinopathy, nephropathy and peripheral neuropathy are used in the UK to inform risk of developing blindness, renal failure, and amputation, respectively. Our findings suggest these data may offer a simple tool to identify very high-risk individuals with type 2 diabetes who are currently perceived to be at lower absolute risk using contemporary risk models.

Cardiovascular risk estimation in diabetes has important implications for primary prevention strategies. The 2013 ACC/ AHA guidelines on the control of blood cholesterol advocate moderate-intensity statin therapy in persons with diabetes who are 40-75 years of age; while high-intensity therapy is restricted to individuals with a ≥7.5% estimated 10-year risk of ASCVD.[3] Our findings suggest that individuals with microvascular disease would be eligible for high-intensity statin treatment based on the recorded event rates. The 10-year risk of MI or ischemic stroke (fatal or non-fatal) in the present study was 10.4% in participants with a single

manifestation of microvascular disease, 15.0% with two, and 22.5% with three microvascular beds affected.

Among individuals with three manifestations of microvascular disease, our data indicate that good control of risk factors (HbA1c <7.0%, low-density cholesterol <100 per decilitre, and blood pressure <140/90) is associated with a halving of the risk of future cardiovascular events than when these factors are not at goal (17.4 versus 32.5 events per 1000 person years). Insights from the Steno-2 study support this observation that aggressive management of risk factors might mitigate some of the excess risk associated with microvascular disease.[27] It randomised patients with type 2 diabetes and persistent microalbuminuria to receive either intensive or conventional therapy for a number of modifiable risk factors including glucose control, blood pressure, total cholesterol and triglyceride levels. Intensive therapy was associated with a lower risk of both fatal and non-fatal cardiovascular events at a median follow-up of 13 years. An important caveat however is that baseline cardiovascular risk factors were significantly more adverse in Steno-2 compared to the present cohort.

We also assessed the associations of microvascular disease burden with hospitalization for heart failure and report event rates around half those observed in the recent Reduction of Atherothrombosis for Continued Health (REACH) registry.[28] Among participants with established atherothrombosis and a prior ischemic event enrolled in REACH, 6.5% of patients were hospitalized for heart failure corresponding to a rate of 16 per 1000 person years. This compared to an overall rate of 6 per 1000 person years in this study of individuals free of cardiovascular disease at baseline. Those with disease in three microvascular beds were at significantly greater risk, with event rates of 15 per 1000 person years, similar to those with a history of MI or stroke in REACH. In comparison with diabetic patients free from microvascular disease, the adjusted hazards for heart failure with the presence of one, two, or three microvascular disease states were 1.53, 2.16, and 3.02, respectively. The mechanisms behind this association are unclear but plausible contributors include CAN, which frequently co-exists with other microvascular disease states,[29] and may be the diabetes-specific process that explains part of the excess risk of heart failure not accounted for by increased burden of atherothrombosis.[30, 31]

While the present data derive from a validated and nationally representative sample of England, results should not be extrapolated to dissimilar populations. Important limitations of the study include our reliance on comprehensive code lists for any given baseline or outcome variable. This is a limitation common to all studies using routinely recorded data and was mitigated through the use of a validated approach for defining baseline and outcome parameters.[16, 19] Analyses were restricted to individuals in whom complete information was available on prevalent microvascular disease and may be subject to selection bias. Examination of the association between microvascular disease and ASCVD among

individuals with data missing on all three diseases showed no qualitative difference with the complete cohort (Supplementary Appendix 13). Results may have been affected by unmeasured variables such as diet, which was not considered in our analyses because these data are unreliably recorded. Finally, the data presented here are observational in nature and although attempts have been made to reduce confounding by statistical adjustment we cannot exclude the possibility of residual confounding as part of the explanation for our findings.

In this linked primary and secondary care study of diabetic adults, microvascular disease was found to confer a risk equivalent to conventional factors including smoking, hypertension and dyslipidaemia. Cardiovascular risk increased with the total number of microvascular beds affected, suggesting a continued broad assessment program for retinopathy, nephropathy and peripheral neuropathy can provide reliable information on cardiovascular risk, in addition to morbidity linked to individual microvascular disease states. Such prognostic data has implications for cardiovascular risk stratification and prevention strategies.

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Table 1. Baseline Characteristics

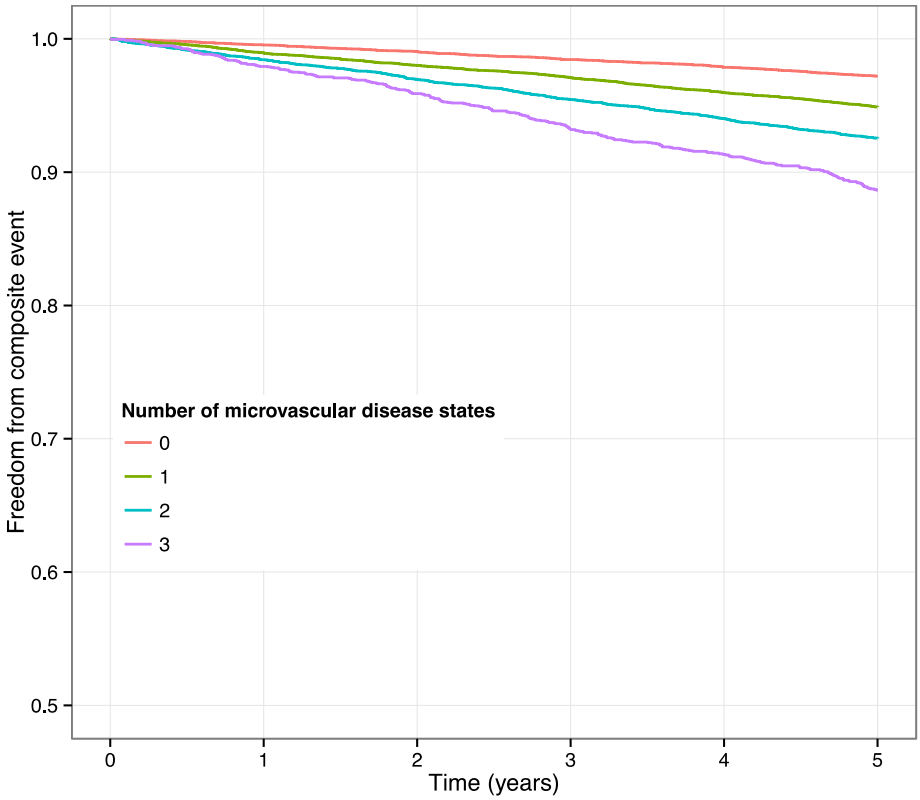
	Number microvascular disease states†				All n=48 367
	0 n=16 280	1 n=19 125	2 n=10 184	3 n=2778	
Age, years	64.8 (11.7)***	69.3 (11.7)	72.0 (11.0)	72.2 (10.7)	68.5 (11.9)
Women	7826 (48.1)***	8637 (45.2)	4284 (42.1)	1083 (40.0)	21830 (45.1)
White ethnicity	4184 (91.0)***	4776 (90.3)	2450 (90.8)	618 (89.4)	12028 (90.6)
BMI, kg/m^2	30.8 (6.2)***	30.6 (6.4)	30.5 (6.2)	30.7 (6.2)	30.7 (6.3)
HbA1c, %	7.18 (1.23)***	7.28 (1.29)	7.45 (1.38)	7.87 (1.57)	7.31 (1.32)
Duration diabetes, years	5.8 (4.5)***	7.7 (5.8)	10.3 (7.0)	14.5 (8.1)	8.0 (6.3)
Systolic blood pressure, mmHg	135.6 (12.8)***	137.1 (13.3)	138.2 (14.5)	139.7 (15.2)	137.0 (13.6)
Diastolic blood pressure, mmHg	77.4 (7.8)***	76.2 (8.1)	74.7 (8.5)	74.0 (8.7)	76.2 (8.2)
Total cholesterol, mmol/L	4.36 (0.90)***	4.28 (0.89)	4.20 (0.89)	4.13 (1.00)	4.28 (0.91)
HDL cholesterol, mmol/L	1.28 (0.36)***	1.27 (0.39)	1.25 (0.39)	1.20 (0.38)	1.26 (0.38)
LDL cholesterol, mmol/L	2.37 (0.86)***	2.29 (0.83)	2.22 (0.82)	2.17 (0.84)	2.29 (0.84)
eGFR, $mL/min/1.73m^2$	75.6 (19.6)***	70.9 (22.6)	64.9 (24.1)	56.9 (23.7)	70.5 (22.6)
Smoking history	11812 (72.6)***	14575 (76.2)	7941 (78.0)	2242 (80.7)	36570 (75.8)
Deprivation index ≤ 5^{th} decile	5898 (54.2)***	7058 (53.6)	3765 (53.6)	1001 (51.4)	17722 (53.7)
Statin use	11472 (70.5)***	13875 (72.5)	7655 (75.2)	2094 (75.4)	35096 (72.6)
ACEi/ARB	10312 (63.3)***	14301 (74.8)	8645 (84.9)	2587 (93.1)	35845 (74.1)
Antiplatelet	9273 (57.0)***	12467 (65.2)	7265 (71.3)	2091 (75.3)	31096 (64.3)

† Microvascular diseases considered include retinopathy, nephropathy and peripheral neuropathy. Data are mean (SD) or number (%). BMI indicates body mass index; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; ACEi/ARB, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker. *P<0.05; **P<0.01; ***P<0.001. P values from Chi square test or ANOVA are provided for the overall trend with increasing number of microvascular disease states. Missing values: The following variables had missing values: Ethnicity (n=35095, 72.6%), BMI (n=82, 0.2%), HbA1c (n=101, 0.2%), Systolic BP (n=15, 0.03%), Diastolic BP (n=15, 0.03%), Total cholesterol (n=38, 0.08%), HDL cholesterol (n=3825, 7.9%), LDL cholesterol (n=8311, 17.2%), eGFR (n=1752, 3.6%), Smoking status (n=123, 0.3%), Deprivation index (n=.15255, 46.5%)

Table 2. Adjusted Hazard ratios of Clinical Outcomes by Burden of Microvascular Disease*

	Number microvascular disease states			
	0 n=16 280	1 n=19 125	2 n=10 184	3 n=2778
Atherosclerotic cardiovascular disease				
N	528 (3.2%)	1064 (5.6%)	799 (7.9%)	298 (10.7%)
Event rate per 1000 person years	5.73	10.37	15.45	22.50
Unadjusted hazard ratio	1.00	1.83 (1.64-2.03)	2.75 (2.46-3.06)	4.03 (3.50-4.65)
Adjusted hazard ratio (95% CI)*	1.00	1.30 (1.16-1.47)	1.64 (1.45-1.87)	2.24 (1.91-2.64)
Hospitalization for heart failure				
N	199 (1.2%)	496 (2.6%)	474 (4.7%)	188 (6.8%)
Event rate per 1000 person years	2.35	5.26	10.01	15.51
Unadjusted hazard ratio	1.00	2.24 (1.90-2.64)	4.26 (3.61-5.03)	6.61 (5.42-8.07)
Adjusted hazard ratio (95% CI)*	1.00	1.53 (1.28-1.82)	2.16 (1.81-2.59)	3.02 (2.43-3.75)
Cardiovascular mortality				
n	145 (1.9%)	346 (4.0%)	277 (6.2%)	131 (11.5%)
Event rate per 1000 person years	1.86	3.97	6.24	11.46
Unadjusted hazard ratio	1.00	2.13 (1.75-2.58)	3.35 (2.74-4.10)	6.16 (4.86-7.80)
Adjusted hazard ratio (95% CI)*	1.00	1.39 (1.14-1.71)	1.73 (1.40-2.16)	2.87 (2.21-3.72)

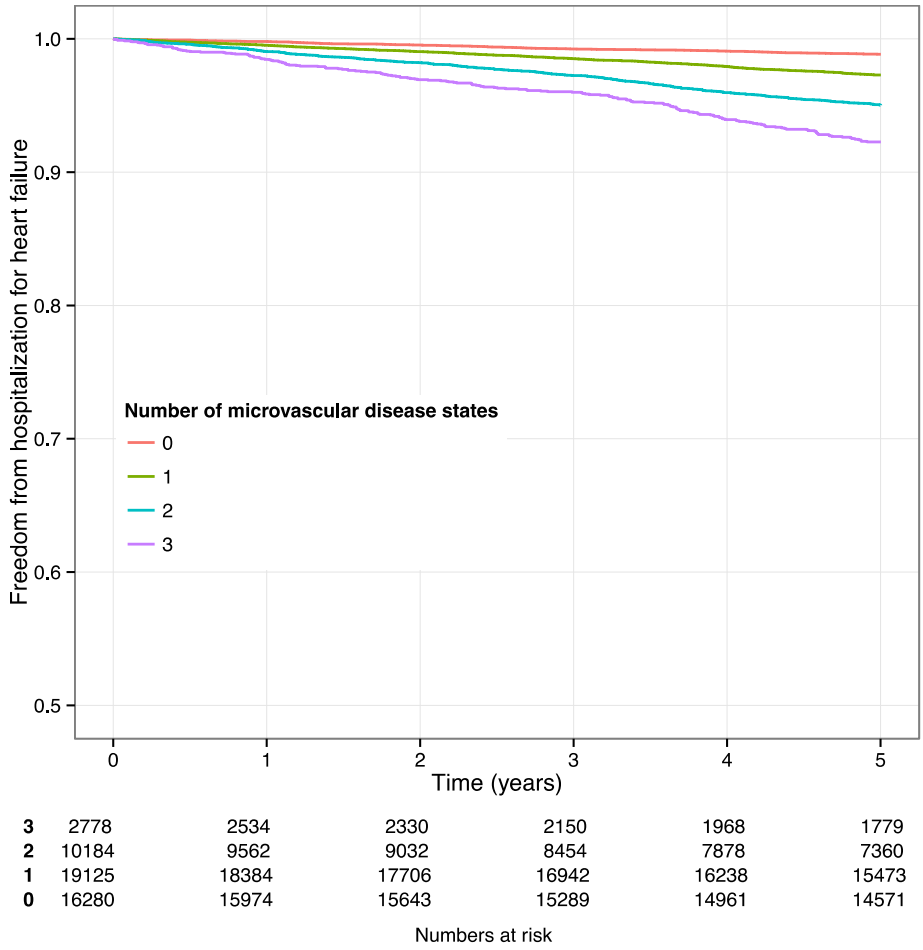
* Adjusted for age, gender, systolic BP, diastolic BP, LDL-C, HDL-C, HbA1c, BMI, CKD, smoking status, index of multiple deprivation, antiplatelet therapy, lipid-lowering and renin angiotensin blockade treatment



3	2778	2536	2326	2115	1942	1751
2	10184	9541	8978	8397	7827	7289
1	19125	18328	17599	16803	16059	15278
0	16280	15944	15605	15232	14861	14427

Numbers at risk

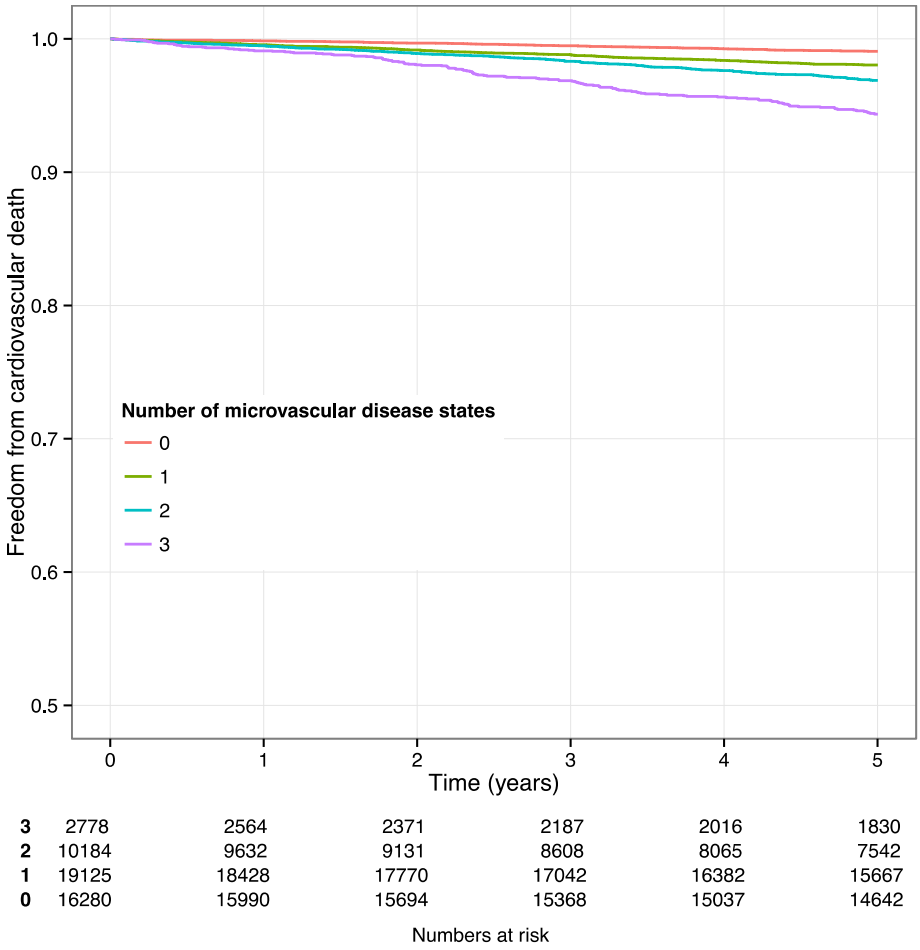
A



3	2778	2534	2330	2150	1968	1779
2	10184	9562	9032	8454	7878	7360
1	19125	18384	17706	16942	16238	15473
0	16280	15974	15643	15289	14961	14571

Numbers at risk

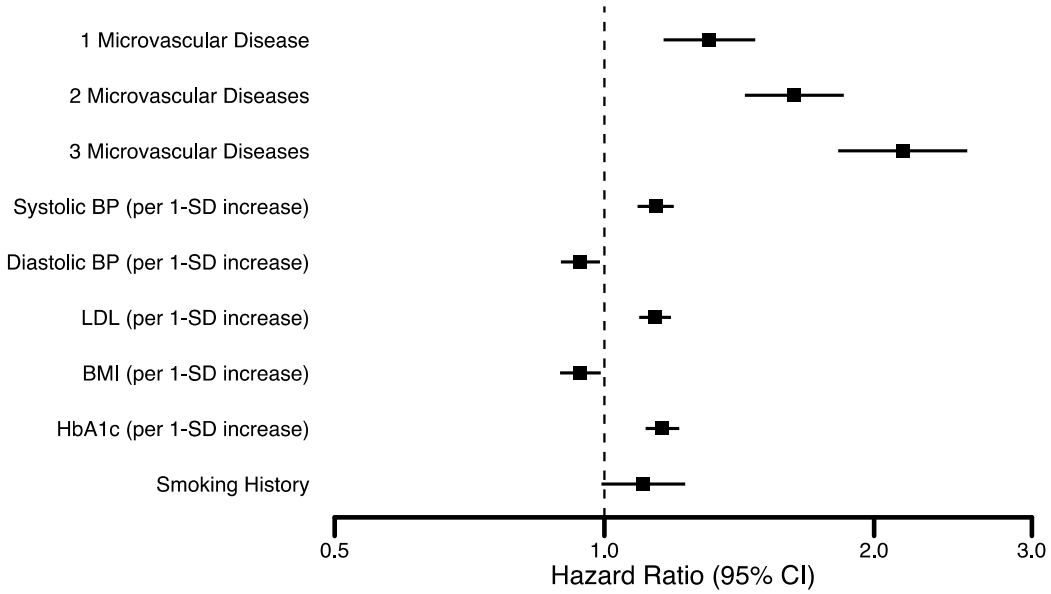
B



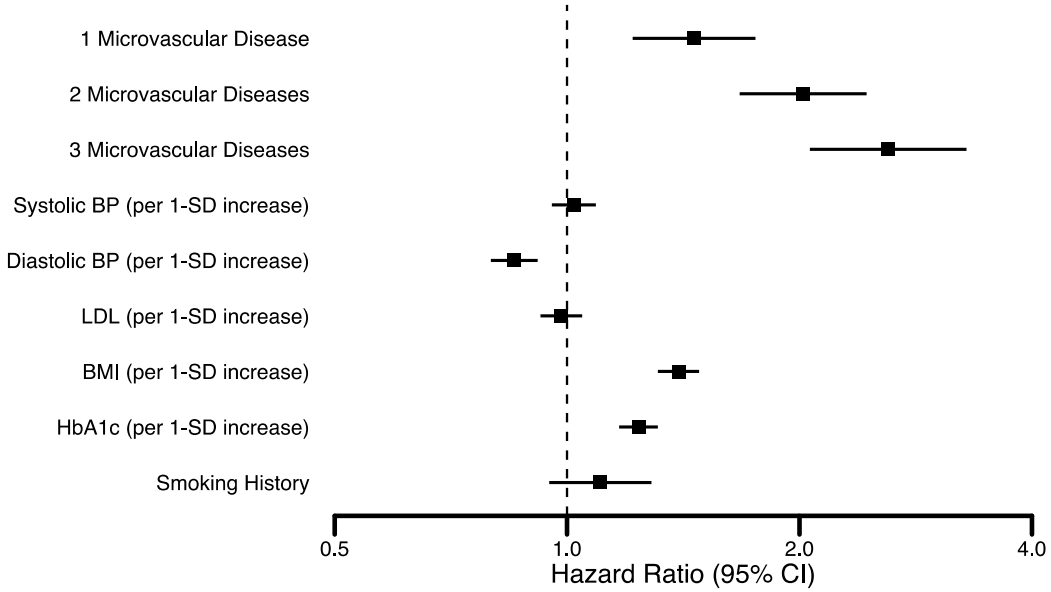
C

Figure 1. Unadjusted freedom from cardiovascular events (A), hospitalization for heart failure (B), and cardiovascular mortality (C) by cumulative burden of microvascular disease.

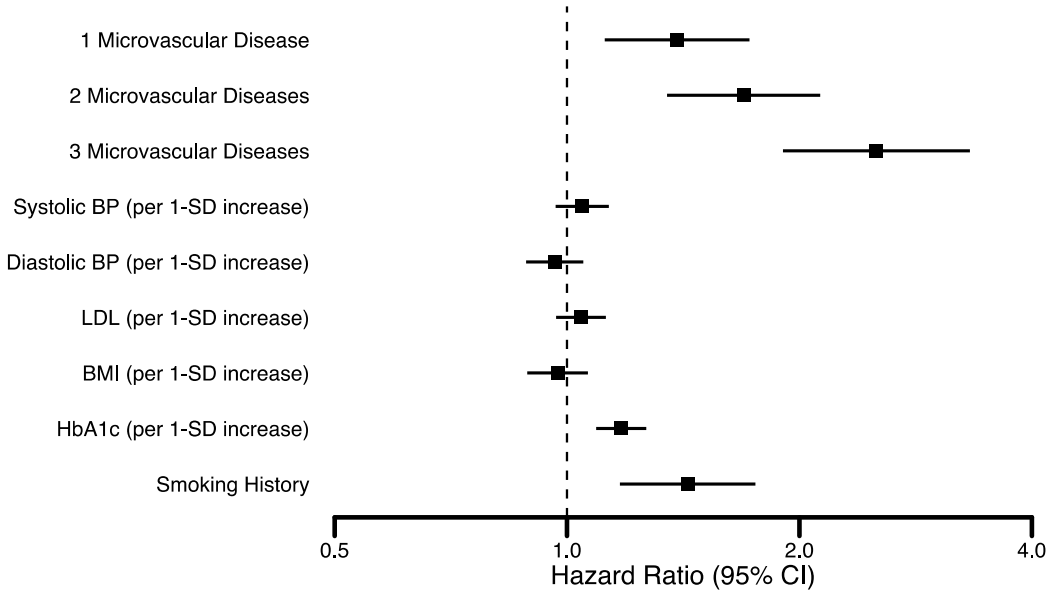
Cardiovascular events defined as fatal and non-fatal events of myocardial infarction or stroke. Log-rank test for the linear association between cumulative burden of microvascular disease for cardiovascular events p<0.001; and for all-cause mortality p<0.001.


1 Microvascular Disease
2 Microvascular Diseases
3 Microvascular Diseases
Systolic BP (per 1-SD increase)
Diastolic BP (per 1-SD increase)
LDL (per 1-SD increase)
BMI (per 1-SD increase)
HbA1c (per 1-SD increase)
Smoking History
0.5
1.0
2.0
3.0
Hazard Ratio (95% CI)

A


1 Microvascular Disease
2 Microvascular Diseases
3 Microvascular Diseases
Systolic BP (per 1-SD increase)
Diastolic BP (per 1-SD increase)
LDL (per 1-SD increase)
BMI (per 1-SD increase)
HbA1c (per 1-SD increase)
Smoking History
0.5
1.0
2.0
4.0
Hazard Ratio (95% CI)

B



C

Figure 2. Adjusted hazard ratio for cardiovascular events (A), hospitalization for heart failure (B), and cardiovascular mortality (C) by cumulative burden of microvascular disease and per 1 SD difference in values for established risk factors*

Cardiovascular events defined as first fatal or non-fatal event of myocardial infarction or stroke; cardiovascular death as first fatal myocardial infarction or stroke. A 1 SD increase from the mean for each established risk factor is: BP >150.6/84.4; LDL >121.0; BMI>36.9 kg/m^2; HbA1c >8.6%.

Adjusted for age, gender, systolic BP, diastolic BP, LDL-C, HDL-C, HbA1c, smoking status, index of multiple deprivation, antiplatelet therapy, lipid-lowering and renin angiotensin blockade treatment

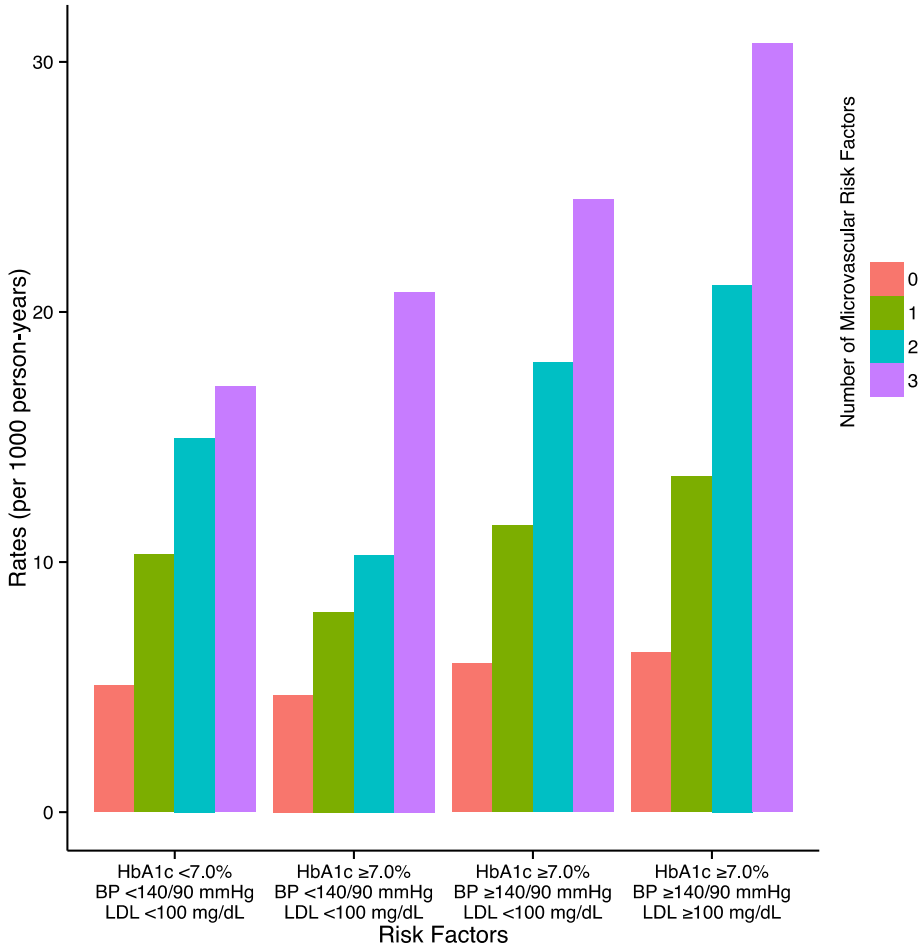


Figure 3. Adjusted cardiovascular event rates by cumulative burden of microvascular disease and established risk factor goals*

Cardiovascular events defined as fatal and non-fatal events of myocardial infarction or stroke.
To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
*Adjusted for age, gender, systolic BP, diastolic BP, LDL-C, HDL-C, HbA1c, smoking status, index of multiple deprivation, antiplatelet therapy, lipid-lowering and renin angiotensin blockade treatment